

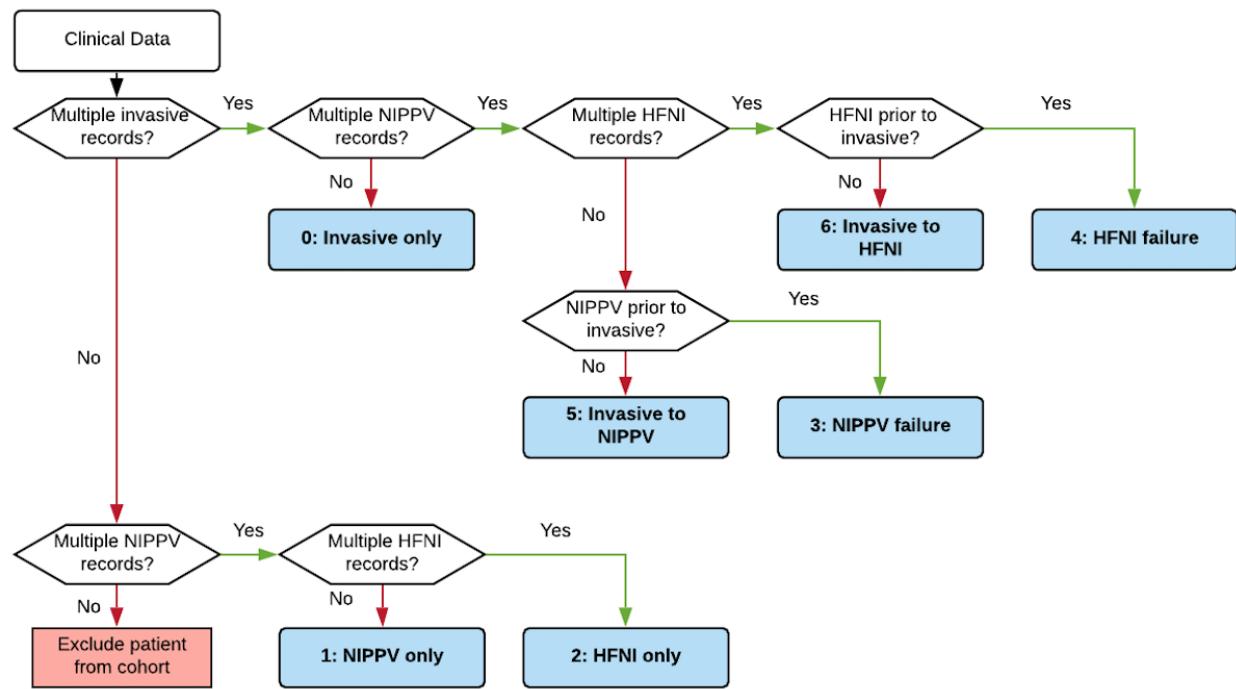
**Validation of an Electronic Phenotyping Algorithm for Patients with Acute Respiratory Failure**

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Supplementary Digital Content

## Methods supplementary content

**Figure 1: Decision-tree model of the phenotyping algorithm**



Abbreviations:

*NIPPV*- noninvasive positive pressure ventilation (includes all terms for continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP)).

*HFNI*- high flow nasal insufflation (includes all terms for heated and humidified high flow nasal oxygen).

**Table 1. ICD codes for primary diagnoses**

<b>Code</b>	<b>ICD-9</b>	<b>ICD-10</b>	<b>Definition</b>
<b>Cardiovascular</b>			
I00-I99		x	Diseases of the circulatory system; excluding I60-69
390-459	x		Diseases of the circulatory system; excluding 430-438
<b>Neurologic/psychiatric/cerebrovascular</b>			
I60-69		x	Cerebrovascular diseases
F00-F99		x	Mental, behavioral and neurodevelopmental disorders
290-319	x		Mental disorders
430-438	x		Cerebrovascular disease
<b>GI</b>			
K00-K95		x	Diseases of the digestive system
520-579	x		Diseases of the digestive system
Endocrine			
E00-E89		x	Endocrine, nutritional and metabolic diseases
240-279	x		Endocrine, nutritional and metabolic diseases, and immunity disorders
<b>Respiratory, all causes</b>			
J00-J99		x	Diseases of the respiratory system
460-519	x		Diseases of the respiratory system
<b>Infectious/allergic/immunologic</b>			
A00-B99		x	Certain infectious and parasitic diseases
001-139	x		Infectious and parasitic diseases
Trauma			
S00-T88		x	Injury poisoning and certain other consequences of external causes
E000-E999	x		Supplementary classification of external causes of injury and poisoning
<b>Renal</b>			
N17-19		x	Acute kidney failure and chronic kidney disease
N25-39		x	Other disorders of kidney and ureter
Z99.2		x	Dependence on renal dialysis
590	x		Infections of kidney
592	x		Calculus of kidney and ureter
593	x		Other disorders of kidney and ureter

**Table 2. ICD codes for comorbidities**

<b>Code</b>	<b>ICD-9</b>	<b>ICD-10</b>	<b>Definition</b>
<b>Heart failure</b>			
I10-I16		x	Hypertensive diseases
I20-I25		x	Ischemic heart diseases
I30-I52		x	Other forms of heart disease
401-405	x		Hypertensive diseases
410-414	x		Ischemic heart disease
420-429	x		Other forms of heart disease
<b>Diabetes</b>			
E08		x	Diabetes mellitus due to underlying condition
E09		x	Drug or chemical induced diabetes mellitus
E10		x	Type 1 diabetes mellitus
E11		x	Type 2 diabetes mellitus
E13		x	Other specified diabetes mellitus
250	x		Diabetes mellitus
249	x		Secondary diabetes mellitus
<b>Chronic kidney disease</b>			
N18		x	Chronic kidney disease
585	x		Chronic kidney disease (ckd)
<b>Chronic liver disease</b>			
K70-K77		x	Diseases of the liver
571	x		Chronic liver disease and cirrhosis
<b>Immunosuppression</b>			
D80		x	Immunodeficiency with predominantly antibody defects
D81		x	Combined immunodeficiencies
D82		x	Immunodeficiency associated with other major defects
D83		x	Common variable immunodeficiency
D84		x	Other immunodeficiencies
D86		x	Sarcoidosis
D89		x	Other disorders involving the immune mechanism, not elsewhere classified
279	x		Disorders involving the immune mechanism
V87.46	x		Personal history of immunosuppressive therapy
<b>Neoplasm</b>			
C00-C14		x	Malignant neoplasms of lip, oral cavity and pharynx
C15-C26		x	Malignant neoplasms of digestive organs

C30-C39		x	Malignant neoplasms of respiratory and intrathoracic organs
C40-C41		x	Malignant neoplasms of bone and articular cartilage
C43-C44		x	Melanoma and other malignant meoplasms of skin
C45-C49		x	Malignant neoplasms of mesothelial and soft tissue
C50		x	Malignant neoplasms of breast
C51-C58		x	Malignant neoplasms of female genital organs
C60-C63		x	Malignant neoplasms of male genital organs
C64-C68		x	Malignant neoplasms of urinary tract
C69-C72		x	Malignant neoplasms of eye, brain and other parts of central nervous system
C73-C75		x	Malignant neoplasms of thyroid and other endocrine glands
C76-C80		x	Malignant neoplasms of ill-defined, other secondary and unspecified sites
C7A		x	Malignant neuroendocrine tumors
C7B		x	Secondary neuroendocrine tumors
C81-C96		x	Malignant neoplasms of lymphoid, hematopoietic and related tissue
D00-D09		x	In situ neoplasms
C10-D36		x	Benign neoplasms, except benign neuroendocrine tumors
D37-D48		x	Neoplasms of uncertain behavior, polycythemia vera and myelodysplastic syndromes
D3A		x	Benign neuroendocrine tumors
D49		x	Neoplasms of unspecified behavior
140-149	x		Malignant neoplasm of lip, oral cavity, and pharynx
150-159	x		Malignant neoplasm of digestive organs and peritoneum
160-165	x		Malignant neoplasm of respiratory and intrathoracic organs
170-176	x		Malignant neoplasm of bone, connective tissue, skin, and breast
179-189	x		Malignant neoplasm of genitourinary organs
190-199	x		Malignant neoplasm of other and unspecified sites
200-209	x		Malignant neoplasm of lymphatic and mematopoietic tissue
210-229	x		Benign neoplasms
230-234	x		Carcinoma in situ
235-238	x		Neoplasms of uncertain behavior
239	x		Neoplasms of unspecified nature
<b>COPD</b>			
J40-J47		x	Chronic lower respiratory diseases
490-496	x		Chronic obstructive pulmonary disease and allied conditions
J96.02		x	Respiratory failure, not elsewhere classified with hypercapnia
J96.1		x	Chronic respiratory failure
J96.2		x	Acute and chronic respiratory failure
518.83	x		Chronic respiratory failure

518.84	x		Acute and chronic respiratory failure
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**Table 3. ICD codes for clinical subgroups**

Code	ICD-9	ICD-10	Definition
<b>Heart failure</b>			
I10-I16		x	Hypertensive diseases
I20-I25		x	Ischemic heart diseases
I30-I52		x	Other forms of heart disease
401-405	x		Hypertensive diseases
410-414	x		Ischemic heart disease
420-429	x		Other forms of heart disease
<b>Asthma</b>			
J45		x	Asthma
J82.83		x	Eosinophilic asthma
493	x		Asthma
<b>COPD</b>			
J40-J47		x	Chronic lower respiratory diseases
490-496	x		Chronic obstructive pulmonary disease and allied conditions
J96.02		x	Respiratory failure, not elsewhere classified with hypercapnia
J96.1		x	Chronic respiratory failure
J96.2		x	Acute and chronic respiratory failure
518.83	x		Chronic respiratory failure
518.84	x		Acute and chronic respiratory failure
<b><i>De novo</i> respiratory failure</b>			
J9-18		x	Influenza and pneumonia
J20-22		x	Other acute lower respiratory infections
J30-39		x	Other diseases of upper respiratory tract
J80-84		x	Other respiratory diseases principally affecting the interstitium
J85-86		x	Suppurative and necrotic conditions of the lower respiratory tract
J96.01		x	Hypoxia
J96.9		x	Respiratory failure, unspecified
A54.84		x	Gonococcal pneumonia
B01.2		x	Varicella pneumonia
Z87.01		x	Personal history of pneumonia
A37.91		x	Whooping cough, unspecified species with pneumonia
R09.02		x	Hypoxemia
480-488	x		Influenza and pneumonia

470-478	x		Other diseases of upper respiratory tract
460-466	x		Acute respiratory infections
799.02	x		Hypoxemia
510-519	x		Other diseases of the respiratory system
98.89	x		Gonococcal infection of other specified sites
33.9	x		Whooping cough, unspecified organism

## Results Supplementary Content

**Table 4: Demographics Summary**

Parameter	Invasive Mechanical Ventilation				NIPPV		High Flow Nasal Oxygen			
	Total IMV	Cohort			Total NIPPV	Cohort		Total HFNO	Cohort	
	0	4	6		1	3		2	5	
	IMV	IMV→NIPPV	IMV→HFNO		NIPPV	NIPPV→IMV		HFNO	HFNO→IMV	
Patients, n	51325	44542	4943	1840	32515	27476	5039	2537	1955	582
Male sex, %	59.6	60.2	57.9	62.4	53.1	53.1	55.5	55.0	53.2	61.0
Age, median (IQR)	64 (51-73)	64 (50-74)	67 (58-75)	63 (51-73)	69 (58-78)	70 (59-79)	66 (56-75)	69 (57-79)	71 (59-81)	64 (52-73)
Race, %										
African American	5.16	4.80	4.50	6.56	5.41	5.14	5.01	4.90	5.24	4.17
Asian	1.07	1.133	0.73	1.15	0.83	0.71	1.14	0.99	0.92	1.56
Hispanic	0.08	0.08	0.06	0.00	0.06	0.07	0.04	0.07	0.00	0.35
Native American	4.51	4.54	2.85	5.20	1.92	1.73	3.10	2.86	1.85	5.73
Other/unknown	4.26	4.49	3.00	4.92	3.19	3.01	3.68	3.54	3.64	3.13
White	84.92	84.95	88.85	82.17	88.59	89.33	87.04	87.64	88.35	85.07
Ethnic group, %										
Hispanic or Latino	17.14	16.92	13.58	22.56	13.65	13.02	16.63	18.06	16.44	21.18
not Hispanic or Latino	82.50	82.64	86.33	77.11	86.21	86.83	83.11	81.63	83.40	77.95
unable or unwilling to answer	0.36	0.44	0.08	0.33	0.14	0.15	0.26	0.31	0.15	0.87
APACHE IVa score on ICU admission*, median (IQR)	64 (47-86)	63 (46-86)	63 (49-80)	75 (54-99)	54 (41-68)	51 (39-63)	68 (53-86)	59 (45-77)	54 (42-68)	72 (54-96)
Primary diagnosis by organ system, n (%)										
Cardiovascular	13886 (27.1)	12249 (27.5)	1274 (25.8)	363 (19.7)	4309 (13.3)	3726 (13.6)	583 (11.6)	242 (9.5)	187 (9.6)	55 (9.5)
Neurologic, psychiatric, cerebrovascular	2276 (4.4)	2068 (4.6)	102 (2.1)	106 (5.8)	611 (1.9)	539 (2.0)	72 (1.4)	66 (2.6)	39 (2.0)	27 (4.6)
Gastrointestinal	3603 (7.0)	3216 (7.2)	288 (5.8)	99 (5.4)	1489 (4.6)	1213 (4.4)	276 (5.5)	129 (5.1)	88 (4.5)	41 (7.0)
Endocrine	1850 (3.6)	1747 (3.9)	78 (1.6)	25 (1.4)	874 (2.7)	782 (2.8)	92 (1.8)	55 (2.2)	48 (2.5)	7 (1.2)
Respiratory, all causes	5499 (10.7)	4464 (10.0)	831 (16.8)	204 (11.1)	7369 (22.7)	6343 (23.1)	1026 (20.4)	452 (17.8)	375 (19.2)	77 (13.2)
Infectious, allergic, immunologic	6010 (11.7)	5205 (11.7)	562 (11.4)	243 (13.2)	4040 (12.4)	3111 (11.3)	929 (18.4)	395 (15.6)	287 (14.7)	108 (18.6)
Trauma	4647 (9.1)	4174 (9.4)	274 (5.5)	199 (10.8)	1402 (4.3)	1159 (4.2)	243 (4.8)	146 (5.8)	99 (5.1)	47 (8.1)
Renal	452 (0.9)	370 (0.8)	54 (1.1)	28 (1.5)	621 (1.9)	552 (2.0)	69 (1.4)	58 (2.3)	50 (2.6)	8 (1.4)
other	13102 (25.5)	11049 (24.8)	1480 (29.9)	573 (31.1)	11800 (36.3)	10051 (36.6)	1749 (34.7)	994 (39.2)	782 (40.0)	212 (36.4)
Comorbidities, n (%)										
Heart failure	3841 (7.5)	3511 (7.9)	261 (5.3)	69 (3.8)	2240 (6.9)	2061 (7.5)	179 (3.6)	98 (3.9)	90 (4.6)	8 (1.4)
Diabetes	7 (0.0)	6 (0.0)	1 (0.0)	0 (0.0)	5 (0.0)	5 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Chronic kidney disease	30 (0.1)	25 (0.1)	5 (0.1)	0 (0.0)	26 (0.1)	26 (0.1)	0 (0.0)	1 (0.0)	1 (0.1)	0 (0.0)
Chronic liver disease	653 (1.3)	536 (1.2)	68 (1.4)	49 (2.7)	192 (0.6)	96 (0.3)	96 (1.9)	15 (0.6)	6 (0.3)	9 (1.5)
Chronic obstructive pulmonary disease	33 (0.1)	31 (0.1)	1 (0.0)	1 (0.1)	61 (0.2)	61 (0.2)	0 (0.0)	3 (0.1)	3 (0.2)	0 (0.0)
immunosuppression and neoplasm	1037 (2.0)	934 (2.1)	84 (1.7)	19 (1.0)	627 (1.9)	538 (2.0)	89 (1.8)	59 (2.3)	47 (2.4)	12 (2.1)
vital signs on treatment assignment, median (IQR)										
Heart rate	84 (73-98)	85 (73-99)	83 (72-96)	90 (75-102)	84 (72-97)	83 (72-96)	87 (74-102)	89 (78-102)	88 (77-100)	94 (82-106)
Systolic blood pressure	120 (106-136)	120 (105-136)	121 (108-137)	118 (103-136)	125 (110-142)	126 (111-143)	118 (104-135)	120 (107-139)	121 (108-140)	116 (104-132)
Diastolic blood pressure	67 (58-78)	67 (58-78)	68 (59-77)	64 (57-75)	70 (60-79)	70 (61-79)	66 (56-76)	67 (59-78)	68 (59-78)	65 (55-78)
Oxygen Saturation (pulse oximetry)	97 (95-99)	97 (95-99)	97 (95-99)	97 (95-99)	96 (94-98)	96 (94-98)	97 (94-99)	95 (93-97)	95 (92-97)	96 (93-98)
Respiratory rate	18 (16-22)	18 (16-22)	18 (16-21)	20 (17-24)	18 (17-22)	18 (17-21)	20 (17-24)	19 (17-24)	18 (17-22)	22 (18-26)
Admit to treatment assignment, hours, median (IQR)	3.98 (1-27)	10.2 (2-36)	17.3 (3-55)	20.0 (4-77)	47.6 (13-110)	45.6 (14-103)	27.1 (7-85)	50.2 (20-114)	50.4 (22-116)	33.4 (12-89)
Vasopressor use, n (%)										
at/before time of treatment assignment	5900 (73.6)	4946 (62.8)	685 (8.7)	269 (3.4)	1762 (23.6)	1195 (15.2)	567 (7.2)	209 (2.85)	110 (1.4)	99 (1.3)
after treatment assignment	9856 (81.8)	8353 (70.3)	914 (7.7)	589 (5.0)	1805 (16.2)	424 (3.6)	1381 (11.6)	229 (1.98)	27 (0.2)	202 (1.7)
Admit location, n (%)										
Non-ICU	152 (0.27)	80 (0.18)	63 (1.28)	9 (0.49)	12651 (36.8)	12620 (45.0)	31 (0.62)	730 (26.8)	723 (37.0)	7 (1.20)
ED to Intensive care unit	20393 (41.3)	17804 (40.0)	1746 (35.4)	843 (45.9)	10558 (35.2)	8489 (30.9)	2069 (41.1)	791 (32.5)	556 (28.5)	235 (40.4)
Operating Room to Intensive care unit	18 778(33.5)	16917 (38.0)	1458 (29.5)	403 (21.9)	1811 (5.07)	1227 (4.47)	584 (11.6)	134 (5.12)	77 (3.94)	57 (9.81)
Medical/surgical unit to Intensive care unit	10299 (21.6)	8407 (18.9)	1388 (28.1)	504 (27.4)	6249 (19.3)	4309 (15.7)	1940 (38.6)	738 (30.0)	502 (25.7)	236 (40.6)
Stepdown unit or outside hospital to intensive care unit	1658 (3.31)	1297 (2.91)	283 (5.73)	78 (4.25)	1227 (3.72)	820 (2.99)	407 (8.09)	141 (5.50)	95 (4.86)	46 (7.91)

IMV= Invasive Mechanical Ventilation

NIPPV= Noninvasive positive pressure ventilation

HFNO= High-flow nasal oxygen

## *Outcomes and Clinical Subgroups*

Patients with a primary cardiovascular diagnosis had failure rates of 14% (583/4309) for NIPPV and 23% (55/242) for HFNO. Patients with primarily respiratory admission diagnoses had failure rates of 14% (1026/7369) and 17% (77/452) for NIPPV and HFNO, respectively. Those with primarily infectious disease diagnoses had failure rates of 23% (929/4040) and 27% (108/395), respectively.

There was minimal difference in total duration of therapy between invasive mechanical ventilation, NIPPV, and HFNO, however, when patients required mechanical ventilation after a trial of NIPPV, the median combined duration of therapy was longer than if they failed HFNO [2.89 days (1-7) vs 1.98 days (1-6)] (See Table 5 below).

**Table 5. Patient outcomes across phenotypes stratified by *all patients and survivors*.**

Outcome	IMV	NIPPV	HFNO	NIPPV→IMV	IMV→NIPPV	HFNO→IMV	IMV→HFNO
Duration of therapy, days, med. (IQR)							
All patients	n/a	0.76 (0-2)	0.83 (0-1)	2.89 (1-7)	2.23 (1-6)	1.98 (1-6)	4.67 (1-11)
Survivors	n/a	0.81 (0-2)	1.43 (0-2)	3.24 (1-7)	2.13 (1-5)	2.21 (1-7)	3.58 (1-11)
Duration of IMV, days, med. (IQR)							
All patients	0.83 (0-3)	n/a	n/a	2.60 (1-6)	1.82 (1-5)	1.92 (1-6)	4.62 (1-11)
Survivors	0.78 (0.2)	n/a	n/a	2.89 (1-6)	1.75 (1-5)	2.16 (1-6)	3.36 (1-11)
ICU LOS, days, median (IQR)							
All patients	7.03 (4-12)	6.10 (4-10)	6.89 (3-12)	11.4 (6-19)	12.8 (8-20)	8.91 (4-17)	10.3 (6-18)
Survivors	7.74 (5-13)	6.22 (4-10)	7.65 (4-12)	13.2 (8-21)	12.8 (8-20)	11.6 (4-19)	11.8 (7-20)
Hospital LOS, days, median (IQR)							
All patients	7.02 (4-12)	5.21 (3-9)	6.48 (3-11)	11.8 (6-20)	12.8 (8-20)	8.88 (3-17)	10.5 (6-18)
Survivors	7.68 (5-13)	6.33 (4-10)	7.38 (4-12)	13.8 (8-22)	12.9 (8-20)	11.6 (4-20)	12.2 (7-20)
All-cause ICU mortality, %	18.8	8.32	28.1	30.6	8.00	60.4	41.3
All-cause hospital mortality, %	18.6	6.58	24.3	31.6	8.07	60.7	43.8
IMV= invasive mechanical ventilation							
IQR= interquartile range							

In each of the clinical subgroups (heart failure, chronic obstructive pulmonary disease, *de novo* respiratory failure, and asthma), HFNO had a higher failure rate (See Table 6 below). Patients with heart failure, COPD, and *de novo* respiratory failure also had higher ICU and hospital mortality rates when treated with HFNO.

**Table 6. Patient outcomes stratified by primary diagnosis clinical subgroup.**

	Heart Failure			COPD			Asthma			De Novo Respiratory Failure		
	IMV	NIPPV	HFNO	IMV	NIPPV	HFNO	IMV	NIPPV	HFNO	IMV	NIPPV	HFNO
First assigned therapy, n (%)	14279	5985	298	1371	3842	146	118	432	12	7018	6374	487
Escalation of therapy, n (%)	-	731 (12.2%)	-	-	456 (11.9%)	-	-	42 (9.7%)	-	-	1051 (16.5%)	-
NIPPV to IMV	-	-	117 (39.3%)	-	-	46 (31.5%)	-	-	0 (0%)	-	-	186 (38.2%)
HFNO to NIPPV or IMV	-	-	72 (24.2%)	-	-	17 (11.6%)	-	-	1 (8.3%)	-	-	96 (19.7%)
HFNO to IMV	-	-	-	-	-	-	-	-	-	-	-	-
Duration of therapy, days, med (IQR)												
all patients	0.327 (0-1)	1.06 (0-3)	0.865 (0-3)	2.00 (1-5)	1.32 (0-3)	0.938 (0-4)	1.31 (0-3)	1.16 (0-2)	2.45 (2-3)	1.65 (1-5)	1.38 (0-4)	1.06 (0-5)
survivors	0.290 (0-1)	1.17 (0-3)	0.572 (0-2)	1.96 (1-5)	1.49 (1-4)	1.53 (0-7)	1.31 (0-3)	1.30 (0-2)	2.45 (2-3)	1.60 (1-4)	1.64 (0-4)	1.51 (0-5)
Duration of IMV days, med (IQR)												
all patients	0.323 (0-1)	1.62 (1-4)	1.47 (0-4)	1.87 (1-5)	1.92 (1-5)	3.24 (1-8)	1.24 (0-3)	1.82 (1-3)	3.47 (3-4)	1.63 (1-4)	2.53 (1-6)	2.94 (1-8)
survivors	0.286 (0-1)	1.70 (1-4)	0.975 (0-3)	1.82 (1-4)	1.89 (1-5)	5.17 (3-11)	1.20 (0-3)	1.67 (1-3)	3.47 (3-4)	1.57 (1-4)	2.60 (1-6)	2.20 (1-7)
Hospital LOS, d, med (IQR)												
all patients	6.65 (5-10)	5.00 (3-9)	5.19 (3-10)	7.59 (5-13)	4.89 (3-8)	6.99 (4-10)	5.12 (3-9)	3.11 (2-5)	5.86 (2-9)	7.93 (4-14)	5.43 (3-9)	7.10 (3-12)
survivors	7.05 (5-10)	4.99 (3-8)	5.22 (3-10)	7.84 (5-13)	4.88 (3-8)	7.23 (5-10)	5.10 (3-9)	3.10 (2-5)	5.86 (2-9)	8.46 (5-15)	5.44 (3-9)	7.81 (4-11)
ICU LOS, d, med (IQR)												
all patients	6.65 (5-10)	5.86 (3-10)	5.84 (3-10)	7.61 (5-13)	5.64 (3-9)	7.54 (5-12)	5.12 (3-9)	3.46 (2-5)	6.69 (6-7)	7.95 (4-14)	6.36 (4-11)	8.14 (3-13)
survivors	7.05 (5-10)	5.86 (3-10)	5.89 (3-11)	7.89 (5-13)	5.64 (4-9)	7.33 (5-11)	5.10 (3-9)	3.44 (2-5)	6.69 (6-7)	8.47 (5-15)	6.44 (4-11)	8.86 (4-13)
All-cause hosp. mortality, %	13.46	6.21	28.97	11.36	9.50	22.14	4.88	0.40	0	16.98	8.56	28.13
All-cause ICU mortality, %	13.46	8.59	34.01	11.31	6.71	22.83	4.88	0.76	0	17.01	11.20	33.92

NIPPV= noninvasive positive pressure ventilation

IMV= invasive mechanical ventilation

HFNO= High-flow nasal oxygen

LOS- length of stay

IQR- interquartile range